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10/672,866	09/26/2003	C. Frank Bennett	ISPH-0788	2637

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EXAMINER
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CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/672,866

Applicant(s)

BENNETT ET AL.

Examiner

Kimberly Chong

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 03/26/04, 12/13/04.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_.

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## DETAILED ACTION

### *Status of the Application*

Claims 1-10 are currently pending and are currently under examination.

### *Specification*

The disclosure is objected to because of the following informalities: The sequence listed on page 130, line 25, does not have a sequence identifier.

Appropriate correction is required.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-2, 4-10 and 15 of copending Application No. 10/633,843.

Claims 1-9 are drawn to an antisense compound, 8 to 50 nucleobases in length, that target nucleobases 96-523, which is essentially the coding region of a nucleic acid molecule (SEQ ID NO:3) encoding human superoxide dismutase 1, and further drawn to said compounds comprising internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) or chimeras.

Claims 1-2 and 4-10 of copending Application No. 10/633,843 are drawn to an antisense compound 8 to 50 nucleobases in length targeted to a coding reading of a nucleic acid molecule encoding human superoxide dismutase 1 (SEQ ID NO: 3) and further drawn to said compounds comprising at least one modified internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) modification. The claims further recite the antisense compound is a chimeric oligonucleotide.

Claims 1-2 and 4-10 of copending Application No. 10/633,843 are drawn to an antisense that broadly targets the coding region of superoxide dismutase 1, which encompasses the targeted region of 96-523 as recited by claims 1-10 of the instant application. Claims 1-2, 4-10 and 15 of copending Application No. 10/633,843 are further recite the antisense compound comprises internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) or chimeras and the instant claims recite the antisense compound comprises internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) or chimeras.

Therefore, claims 1-2 and 4-10 of copending Application No. 10/633,843 anticipate claims 1-9 of the instant application.

This is a provisional obviousness-type double patenting rejection.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites an antisense compound that “specifically hybridizes”, but does not indicate what the antisense compound hybridizes with (see claim 1, line 4). It is unclear whether the antisense compound hybridizes with a nucleic acid encoding human superoxide dismutase, soluble, or with a protein product of a nucleic acid encoding human superoxide dismutase, soluble, or any other cellular product. Claims 2-9 are indefinite for the same reasons as above, due to their dependence on claim 1.

It is suggested the claim state, “a nucleic acid molecule (SEQ ID NO: 3) encoding human superoxide dismutase 1, soluble”.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting human superoxide dismutase 1 in cells *in vitro*

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and enabling for a method of inhibiting human superoxide dismutase 1 in a rat following intraventricular administration of an antisense targeted to rat superoxide dismutase 1, does not reasonably provide enablement for a method of inhibiting human superoxide dismutase 1, soluble, in any cell or tissue of any animal by administration of an antisense targeted to human superoxide dismutase 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The instant claim is broadly drawn to a method of inhibiting expression of superoxide dismutase 1 in the brain or spinal cord cells or tissues of any animal by administration of an antisense targeted to human superoxide dismutase 1.

The specification as filed discloses a method of inhibition of superoxide dismutase 1 in cells, *in vitro*, by administration of an antisense targeted to a gene encoding human superoxide dismutase 1, soluble (see Example 15) or targeted to a gene encoding rat superoxide dismutase 1, soluble (see Example 19). The specification further discloses inhibition of rat superoxide dismutase 1 in a rat brain after intraventricular administration of an antisense targeted to rat superoxide dismutase 1 (see Example 22). The specification as filed does not disclose that because of administration of an antisense compound targeted to any superoxide dismutase 1 gene, superoxide dismutase 1 is inhibited in any brain or spinal cord cells or tissue.

There is no guidance in the specification as filed that teaches how to target the claimed antisense compound to brain or spinal cord cells or tissues in any animal and inhibit the expression of human superoxide dismutase 1, *in vivo*, in any animal. Although the specification discloses inhibition of human and rat superoxide dismutase 1, *in vitro*, by administration of

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antisense compound and discloses inhibition of rat superoxide dismutase 1 in a rat brain after intraventricular administration of an antisense targeted to rat superoxide dismutase 1, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claim 10 encompasses a method of inhibition of any superoxide dismutase 1 in any brain or spinal cord cell or tissue, by administration of an antisense targeted to a gene encoding superoxide dismutase 1, soluble (see Example 15, 19 and 22), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds. Branch stresses that “because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells” (TIB 23: 45-50 1998). Green *et al.* states that “[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients,

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the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects” (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2).

Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) points out the difficulties of extrapolating from *in vitro* experiments and states on p. 3, paragraph 2, “extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted].”

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that “[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2).” Jen *et al.* concludes that “[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column).”

Moreover, delivery of antisense compounds intraventricularly does not overcome the unpredictability in the antisense art for therapeutic *in vivo* applications. Grzanna *et al.* (Molecular Brain Research, 1998) notes that “Intraventricular injections required delivery of

significantly greater amounts to achieve tissue penetration.” (see page 49, column 1). Grzanna *et al.* further states that “... a large percentage of the ODNs delivered into the lateral ventricle is likely to be flushed out of the ventricle due to rapid [central spinal fluid] CSF flow before it can enter periventricular tissue.” (see page 49, column 1). Grzanna *et al.* concludes that “...the presence of ODNs in tissue by itself cannot be taken as a reliable indicator of their ongoing biological activity.” (see page 49, column 1).

Further, Mirsa *et al.* (J Phar Pharmceutic Sci, 2003) states in general that intraventricular delivery of *any* drug “...has not lived up to its theoretical potential for several reasons. These include slow rate of drug distribution within the CSF and increase in intracranial pressure associated with fluid injections of infusion into small ventricular volumes.” (see page 265, column 1). Mirsa *et al.* further comments that “...[t]he success of this approach is limited by the CSF-brain barrier, composed of barriers to diffusion into brain parenchyma.” (see page 265, column 1).

As outlined above, it is well known that there is a high level of unpredictability in the antisense art for therapeutic *in vivo* applications and intraventricular delivery of antisense compounds does not overcome the unpredictability in the art. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely inhibition of expression of any superoxide dismutase 1, soluble in any brain or spinal cord cell or tissue by administration of an antisense compound targeted to a any gene encoding superoxide dismutase 1, soluble.

While one skilled in the art may be able to find an antisense oligonucleotide targeted to a gene encoding superoxide dismutase 1, soluble and demonstrate inhibition of superoxide

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dismutase 1, soluble, *in vitro*, by using the antisense oligonucleotide, the specification as filed does not teach how to administer any antisense oligonucleotide to any brain or spinal cord cell or tissue of any animal, as claimed.

In view of the unpredictability in the art of antisense-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention in any animal without undue experimentation. Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene.

The claims are drawn broadly to administering to *any* animal an antisense targeting *any* superoxide dismutase 1, soluble sequence. In order to practice the claimed invention, over the full scope claimed, one of skill in the art would have to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include determination of what specific cells to target with superoxide dismutase 1, soluble, how to specifically deliver antisense to a target cell *in vivo* at a concentration effective to result in inhibition of the expression of superoxide dismutase 1, soluble, and what specific diseases and conditions would be treated by the inhibition of superoxide dismutase 1 soluble. Additionally, this undue experimentation would include determination of such factors as dosage *in vivo*, disposition of the antisense molecule in tissues *in vivo* and stability of the antisense molecule *in vivo*.

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Therefore, due to the broad scope of the method claimed, the state of the art of antisense and the level of unpredictability of *in vivo* therapeutic application using antisense, one skilled in the art would not be able to practice the method of claim 10 over the full scope claimed without undue trial and error experimentation.

***Claim Rejections - 35 USC § 102 or 35 USC § 103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2 are rejected under 35 U.S.C. 102(b) or 35 U.S.C. 103(a) as being anticipated by or obvious over Chenchik *et al.* (Patent No: 5,994,076).

The instant claims are drawn to a compound 8 to 50 nucleobases in length targeted to the nucleobases 96-523, which is essentially the coding region, of a nucleic acid molecule (SEQ ID

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NO: 3) encoding human superoxide dismutase 1, soluble wherein the compound specifically hybridizes with and inhibits expression of human superoxide dismutase 1.

Chenchik *et al.* teach a compound, 28 nucleobases in length (SEQ ID NO: 1011) targeted to nucleobases 106-133 of a nucleic acid molecule (SEQ ID NO: 3) encoding human superoxide dismutase 1, soluble (see specification, column 56). The nucleic acid sequence taught by Chenchik *et al.* meets the structural limitation of claims 1-2 of the instant application and would be expected to specifically hybridize to a nucleic acid encoding of human superoxide dismutase 1. Furthermore, since the prior art antisense compound meets all the structural limitations of the claims, the prior art antisense would then be considered to “inhibit expression” of the gene as claimed, absent evidence to the contrary. See, for example, MPEP 2112, which states “[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. “There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.” *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

Thus, the instant claims are anticipated or obvious over Chenchik *et al.*

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by or obvious over Brown *et al.* (Patent No: 5,849,290).

The instant claims are drawn to a compound 8 to 50 nucleobases in length targeted to the nucleobases 96-523 of a nucleic acid molecule (SEQ ID NO: 3) encoding human superoxide dismutase 1, soluble wherein the compound specifically hybridizes with and inhibits expression of human superoxide dismutase 1.

Brown *et al.* teach a compound, 20 nucleobases in length (SEQ ID NO: 10) targeted to nucleobases 298-317 of a nucleic acid molecule (SEQ ID NO: 3) encoding human superoxide dismutase 1, soluble (see specification, column 44-45). The specification states: "...a sequence antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable...". Therefore, the nucleic acid sequence taught by Brown *et al.* meets the structural limitation of claims 1-2 of the instant application and would be expected to specifically hybridize to a nucleic acid encoding of human superoxide dismutase 1.

Furthermore, since the prior art antisense compound meets all the structural limitations of the claims, the prior art antisense would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to

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product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

Thus, the instant claims are anticipated or is obvious over Brown *et al.*

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haung (Patent No: 5,994,076), in view of Baracchini (U.S. Patent NO: 5,80,1154) and in further view of Bennett *et al.* (U.S. Patent NO: 6,077,833).

The invention of the above claims is drawn to antisense compounds, 8 to 50 nucleobases in length, that target nucleobases 96-523 of a nucleic acid molecule (SEQ ID NO: 3) encoding human superoxide dismutase 1, and further drawn to said compounds comprising internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) or chimeras.

Huang *et al.* teach an antisense compound targeted to a nucleic acid molecule encoding human superoxide dismutase 1, soluble (see page 393, Figure 4). Huang *et al.* do not teach antisense sequences specifically targeting nucleotides 96-523 and further comprising internucleoside linkage, nucleobase, and 2' modifications or chimeras.

Baracchini *et al.* teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. These specific examples taught by Baracchini et al include the presently claimed phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8-10. Column 4 teaches various carriers for antisense delivery. Baracchini *et al.* also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett *et al.* are considered to parallel those of Baracchini *et al.* Bennett *et al.* teaches general antisense targeting guidelines at columns 3-4. Bennett *et al.* also teaches targeting coding regions of a desire target, which encompass nucleotides 96-523 of the

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instant claims. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 6-7 teach that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, among others. Columns 7-8 teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. Bennett *et al.* also teach one of ordinary skill to modify nucleobases in antisense oligonucleotides, including the teaching of 5-methylcytosine (col. 8-9), and also to use chimeric antisense oligonucleotides (col. 9-10). Bennett *et al.* teach that the above modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Table 1 teaches the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification). Thus, Bennett *et al.* is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

It would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini *et al.* and Bennett *et al.* into said antisense compounds, as taught by Huang *et al.*

One would have been motivated to create such compounds because Huang expressly teach antisense compounds that target and hybridize to human superoxide dismutase 1, soluble (applicants' SEQ ID NO: 3). One would have been motivated to modify said antisense compounds as taught by Baracchini *et al.* and Bennett *et al.*, because both teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to

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degradation. Further, one would have been motivated to create and modify such compounds because Bennett *et al.* teach antisense compounds that specifically target a desired gene can be used to elucidate the function of the particular gene.

Finally, one would have a reasonable expectation of success because Baracchini *et al.* and Bennett *et al.* both teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

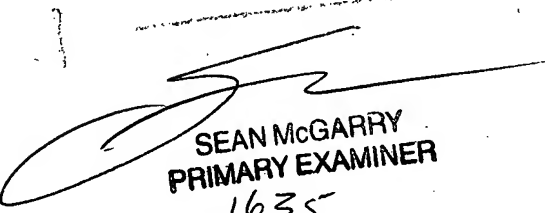
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Kimberly Chong  
Examiner  
Art Unit 1635

  
SEAN MCGARRY  
PRIMARY EXAMINER  
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